

REMARKS

Upon entry of the foregoing amendment, claims 88-90, 98, 105, 109, 116-119, 160, 163, 164 and 167 are pending in this application. Claims 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170, 171, 173, 174, 176, 177, 179, 180, 182, 183 and 185-199 have been withdrawn from consideration as being directed to a non-elected invention. Claims 1-87, 91-97, 120-126, 131-137, 142-148, 153-159, 161, 165, 169, 172, 175, 178, 181 and 184 have been previously canceled without prejudice or disclaimer of the canceled subject matter. Applicant maintains the right to file one or more continuation or divisional applications on any canceled subject matter.

Claim Rejections - 35 USC § 103(a)

1. Claims 88-90 stand rejected as being obvious over a new combination of references: Ulrich et al.¹ and Disis et al.² The Examiner alleges that because MPL and GM-CSF are art-recognized adjuvants, it would have been obvious to one of ordinary skill in the art to combine them into one composition to enhance the immune response against an antigen of interest. Applicant traverses the rejection.

Obviousness – Combining References

Most if not all inventions arise from a combination of old elements. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453,1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. *See id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. *See id.* Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *See In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). It is impermissible to use the claims as a framework from which to pick

¹ Ulrich et al. Monophosphoryl lipid A as an adjuvant. Past experiences and new directions. In M.F. Powell and M.J. Newman (ed.), *Vaccine Design: The Subunit and Adjuvant Approach*. (Plenum Press, New York, 1995), pp. 495-523.

² Disis et al. Granulocyte-Macrophage Colony-Stimulating Factor: An Effective Adjuvant for Protein and Peptide-Based Vaccines. *Blood*, Vol. 88, No. 1 (July 1, 1996), pp. 202-210.

and choose among individual references to recreate the claimed invention. *See In re Fine*, 5 USPQ2d 1586, 1600 (Fed. Cir. 1988).

The motivation, suggestion or teaching may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved. *See WMS Gaming, Inc. v. International Game Tech.*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). However, there still must be **evidence** that “a skilled artisan, confronted with the same problems as the inventor **and with no knowledge of the claimed invention**, would select the elements from the cited prior art references for combination in the manner claimed.” *In re Rouffet*, 47 USPQ2d at 1456; *see also In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (“[a] rejection cannot be predicated on the mere identification . . . of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, *with no knowledge of the claimed invention*, would have selected these components for combination in the manner claimed.”) (Emphasis added.)

The Claimed Invention

Claim 88 is directed to an antigenic composition consisting of an antigen and an effective adjuvanting amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) GM-CSF, together with a diluent or carrier (i.e., a vehicle for the antigen and adjuvants). Claim 89 recites that the antigen is a polypeptide, peptide or fragment derived from a protein. Claim 90 recites that the 3-O-deacylated monophosphoryl lipid A is used in the form of a stable oil-in-water emulsion.

The Cited References

Ulrich et al. disclose that the immunostimulant MPL delivered in aqueous admixtures, in oil-in-water emulsions, or in liposomal vehicles, has adjuvant activity when used alone or in combination with trehalose dimycolate (TDM) or cell wall skeleton (CWS) (pages 509-512). The authors do not disclose or suggest, as the Examiner alleges, that a formulation of antigen and MPL could also include an immunomodulator such as a cytokine, as a second adjuvant. Cytokines, including GM-CSF, are highly defined and specific immunomodulators that, unlike TDM or CWS, are much safer in that they do not elicit inflammatory responses, as do TDM and CWS.

Disis et al., published one year after Ulrich et al., found GM-CSF to be an excellent adjuvant for the elicitation of immunity to both foreign proteins and tumor antigen derived peptides. The authors also found that GM-CSF compared favorably with two "standard" adjuvants, namely complete Freund's adjuvant (CFA) and alum. Disis et al., however, did not combine GM-CSF with those or any other adjuvants. Nor did they consider delivering GM-CSF in a form that was anything but soluble, i.e., they did not consider emulsions for delivery of GM-CSF (such as the SE component of MPLSE).

Rather than pointing to specific information in Disis et al. that suggests its combination with Ulrich et al. to yield the claimed invention, the Examiner merely discusses how the cited references can be combined to read on the claimed invention. This reference-by-reference, limitation-by-limitation analysis wholly fails to demonstrate how the cited references teach or suggest the combination claimed in the present invention. *In re Dembiczak*, 50 USPQ2d 1614, 1618 (Fed. Cir. 1999). At best, one skilled in the art might find it obvious to try various combinations of these known adjuvants to achieve the claimed invention, but this is not the standard of 35 USC §103. (*In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, the adjuvant effect of MPL is formulation-dependent. The Examiner is reminded that Boon et al.'s³ composition did not contain GM-CSF because they found that it was "unable to enhance the effect of the QS21/MPL adjuvant." (See Applicant's April 6, 2006 amendment.)

In view of the foregoing, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness. The rejection, therefore, is improper and should be withdrawn.

2. Claims 88, 98 and 116-119 stand rejected as being obvious over Ulrich et al. and Disis et al., as applied to claim 88, in view of Bartlett et al.⁴

Ulrich et al. and Disis et al. were discussed above. The Examiner has added Bartlett et al. to the mix because they evaluate the safety and immunogenicity of a polyvalent HIV envelope synthetic peptide immunogen, C4-V3, which has the same

³ WO 98/57659, the primary reference previously cited by the Examiner and overcome by Applicant.

⁴ Bartlett et al. Safety and immunogenicity of an HLA-based HIV envelope polyvalent synthetic peptide immunogen. *AIDS*, Vol. 12, No. 11 (1998), pp. 1291-1300.

amino acid sequence set forth in Applicant's SEQ ID NO:2. That the Bartlett trial used Applicant's peptide immunogen is not surprising since it was Applicant (then known as Wyeth-Lederle Vaccines and Pediatrics, Inc.) who co-sponsored the study and provided the C4-V3 immunogen for the study. (See Bartlett et al. at the bottom of page 1291 and at page 1292, right column). Nonetheless, since the combination of Ulrich et al. and Disis et al. does not render the claimed invention obvious, adding Bartlett et al. to the combination does not change the result. There is nothing in the cited references to suggest to the skilled artisan – not to the Examiner having Applicant's specification in hand – that the adjuvant combination of MPLSE and GM-CSF would have been obvious at the time the claimed invention was made.

While the use of adjuvants to enhance the immunogenicity of antigens may be routinely practiced in the art as the Examiner asserts, the selection of which adjuvant(s) to use with a particular antigen in a composition is far from routine. Indeed, Disis et al. state at page 209, left column, last paragraph: "There are many adjuvants effective in eliciting antibody and T-cell responses to foreign proteins. A more critical issue for developing vaccine therapy for human malignancy is whether adjuvants can elicit T-cell responses to proteins or peptides derived from self tumor antigens." On page 1292, top left, Bartlett et al. state: "Efforts to develop effective HIV vaccines have been hampered by lack of knowledge of the correlates of protective immunity to HIV and lack of a strategy to confront the extraordinary diversity of HIV quasi-species."

Most adjuvants do not elicit high titer responses; nor do they elicit CTL responses. Applicant's adjuvant combination, however, elicits high titers and CTL responses, as shown in the instant specification.

Applicant submits that this rejection is also improper and should be withdrawn.

3. Claims 88, 98, 105, 109, 116, 160, 163, 164 and 167 stand rejected as being obvious over Ulrich et al. and Disis et al., in view of Bartlett et al., as applied to claims 88, 98 and 116. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to administer the HIV antigen of Bartlett et al. with the adjuvant composition allegedly taught by combining Ulrich et al. and Disis et al. Applicant disagrees and traverses the rejection.

Claims 105, 109, 160, 163, 164 and 167 depend directly or indirectly from independent claim 88. Claim 88 is directed to an antigenic composition consisting of an antigen and an effective adjuvanting amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) GM-CSF. Dependent claims 105, 160 and 163 recite the administration of the antigenic composition of claim 98 (wherein the antigen is from a pathogenic virus) to a vertebrate host to elicit an immune response in the host. Dependent claim 116 recites that the antigen is from human immunodeficiency virus (HIV). Dependent claims 109, 164 and 167 recite the administration of the antigenic composition of claim 98 to a vertebrate host to elicit cytotoxic T lymphocyte responses in the host.

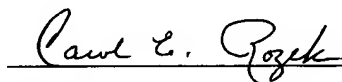
As discussed above, the combination of Ulrich et al. and Disis et al. in view of Bartlett et al. does not render the claimed invention obvious. For the sake of brevity, Applicant does not repeat the rationale here. Suffice it to say, since independent claim 88 is not rendered obvious by the combination of cited references, dependent claims 98, 105, 109, 116, 160, 163, 164 and 167 are likewise not obvious.

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, and therefore, requests that this rejection be withdrawn.

Conclusion

In conclusion, this reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

Respectfully submitted,



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